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Clinical Conditions And Cardiac Function: Correlations With Left Atrial Fibrosis By Mri In Subjects With And Without Atrial Fibrillation

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Clinical Conditions and Cardiac Function: Correlations with Left Atrial Fibrosis by MRI in Subjects with and without Atrial Fibrillation

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Abstract:

The purpose of this study was to evaluate the clinical conditions and cardiac functions associated with left atrial (LA) fibrosis by late gadolinium enhancement (LGE). LA LGE has been found to be associated with various measures of cardiac functions, procedural outcomes, and adverse events in patients who already have atrial fibrillation (AF). Assessment of LA fibrosis by LGE in patients without AF has largely been unexamined and comparison of these patients to those with AF could prove useful. This study was a retrospective chart and imaging review of 137 consecutive subjects imaged with a 3D LGE sequence at one institution from 2012-2014. Fibrosis by LA LGE is elevated in subjects with congestive heart failure (CHF), AF, hypertrophic cardiomyopathy (HCM), and mitral regurgitation when compared to a set of reference subjects (all $p < 0.05$). In multivariate analysis, HCM ($p = 0.01$) and CHF ($p < 0.01$) were independently associated with elevated LGE. Across all subjects, LA LGE was moderately correlated with minimum LA volume ($r = 0.41$, $p < 0.01$) and LA ejection fraction ($r = -0.43$, $p < 0.01$) but weakly correlated with maximum LA volume ($r = 0.197$, $p = 0.02$); these relationships were similar in subgroups with and without AF. In a subset of subjects without AF, there was a lower active atrial ejection fraction with increasing LA LGE ($r = -0.438$, $p < 0.01$). Also, after multivariate adjustment for ventricular filling measures, there was an independent association of increased LA LGE with decreased passive LA emptying ($p = 0.02$). Subjects with heart failure but ventricular ejection fraction >45% had greater LA LGE than those with whose ejection fraction was <45% ($p = 0.03$).

We found that extent of LGE correlates with the presence of CHF, AF, HCM, mitral regurgitation, and some cardiac anatomic and functional measurements. This study lays the groundwork for further evaluation of the utility of measuring LA LGE in patients without AF.

Acknowledgements

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Table of Contents

Introduction

Atrial Fibrillation: Prevalence and Pathogenesis

Atrial fibrillation (AF) is the most common sustained arrhythmia in patients worldwide. In the United States, over 3 million people were estimated to have AF in 2005 with a continuing increase in prevalence that could reach 7 million by 2050[1]. AF has an incidence that increases with age and is associated with symptoms of palpitations, dyspnea (when associated with congestive heart failure (CHF)) and thromboembolic disease. The increased risk of thromboembolic disease results from ineffective atrial contraction caused by the disorganized electrical activity in the atria and associated stasis of the atrial blood. Stroke, visceral, and peripheral ischemia are significant contributors to AF related morbidity and mortality. Clinical management of AF is based on either heart rate or rhythm control, and management of thromboembolic risk with anticoagulants such as warfarin or newer factor X inhibitors. This management carries its own risk of bleeding, which must be carefully weighed against risks of thromboembolism.

The pathogenesis of AF is related to a trigger (an abnormal focus of electrical generation) and a substrate (the atria). It is known that the trigger is closely associated with the pulmonary veins as electrophysiological studies have determined this area is capable of repetitive firing, and the veins have been found to be the site of stretch sensitive ion channels[2,3]. Once triggered, the substrate must have some qualities that allow the electrical activity to persist, or else it would self extinguish. Atrial tissue has a very short action potential

duration and a short refractory period that becomes even shorter with an increasing rate of depolarization[4]. These qualities alone make the atria an ideal site for maintaining aberrant electrical activity. Additionally, atrial remodeling is thought to contribute to abnormal conduction pathways in the atria that lead to the development of self-sustaining rotors of spiraling electrical activity[3,4]. While some remodeling from other cardiac disease *may* contribute to the initial development of AF, episodes of AF are known to contribute to remodeling in a way that reinforces aberrant electrical activity[5] and alters electrophysiological properties of the atrial tissue[6]. This is why paroxysmal AF tends to progress to persistent AF which then becomes harder to terminate and manage from the physician's standpoint.

Remodeling of the left atrium (LA) on pathology studies has been shown to be associated with a variety of cardiac conditions, including AF[5,7,8], mitral regurgitation[9,10], and CHF[11]. Many of these studies have been necropsy studies or been done in animal models as, until relatively recently, there was no way to quantify atrial fibrosis in vivo. As these conditions have significant overlap with the clinical risk factors of AF development mentioned later, there could be potential value in determining whether atrial fibrosis could be used as an independent risk factor for later AF development or used as a guide to disease management by a physician.

Left Atrial Fibrosis by MRI: Late Gadolinium Enhancement

Within the last 10 years, cardiac MRI sequences with late gadolinium enhancement (LGE) have been developed that can examine atrial fibrosis[12]. To

briefly discuss the imaging methodology, in MRI studies, gadolinium is administered as a chelated ion that shortens the relaxation time of nearby protons on T1 weighted sequences in the areas where the molecule in concentrated. Immediately after IV administration, the concentration of gadolinium is highest in the blood when compared to other tissues. However, after time for mixing throughout the blood pool, the gadolinium compounds redistribute into the extracellular space, particularly in regions of tissues that are fibrotic or edematous. In cardiac imaging, scan parameters can be chosen that "null" normal cardiac tissue causing it to have low signal intensity, while areas of myocardium accumulating gadolinium have increased signal intensity. On an image, these areas appear dark or bright (respectively). This technique has long been used in cardiac MRI to examine regions of the ventricle affected by prior infarction, sarcoidosis, and various other forms of cardiomyopathy.

Technical limitations of cardiac MRI limited the ability to use this technique in the thin-walled atria until more recently. The heart is almost always in motion either from its own electro-mechanical pumping function or nearby motion of the lungs and diaphragm. Although there are times during the cardiac cycle when it is moving less rapidly, this motion has always presented a challenge to the spatio-temporal resolution of cardiac MRI, particularly in patients with arrhythmia. To minimize these effects, gating techniques that utilize a subject's EKG and chest diameter ensure cardiac imaging data are acquired within a narrow range of acceptable boundaries, in the current technique, when cardiac motion is minimal. Additionally, many common MRI sequences acquire imaging data in an

xy plane using phase and frequency encoding with a slice selection pulse. In order to accurately identify and quantify late gadolinium enhancement in the atria, data need to be acquired throughout the entire atria concurrently, which requires encoding and acquisition in the x, y, and z dimensions simultaneously. This 3D technique with the aforementioned gating to select for mid-late ventricular diastole is used to image the entire left atrium for areas of T1 enhancement due to accumulation of extracellular gadolinium (see Figures 1B, 2).

LGE on cardiovascular MRI has been used to characterize areas of fibrosis in the LA in patients with atrial fibrillation and has been associated with various metrics and outcomes[12,13]. For example, LA LGE both before and after pulmonary vein isolation is associated with rates of AF recurrence[14,15]. Areas of LGE have been associated with lower endocardial voltage[16,17]. Additionally, greater LA LGE has been found to be associated with stroke risk[18], time in AF, pattern of AF[19], and changes in atrial functional measurements[20]. This LGE detected fibrosis is suspected to underlie the remodelling previously described, which leads to the persistence of aberrant electrical activity in the atria in patients with AF. However, it has yet to be firmly demonstrated that locations of atrial fibrosis are directly correlated with locations of self-sustaining rotors of electrical activity.

Risk factors for Atrial Fibrillation

Current theory regarding the development and maintenance of AF is complex but, as described above, is generally understood as an interaction

between impulses generated by aberrant tissue in the region of the pulmonary veins and a remodeled, fibrotic, and electrically susceptible atrial substrate[3,5]. LA LGE is a noninvasive measurement of one of these AF drivers but its association with risk of developing AF has not been described.

Many different clinical factors have been tied to the risk of developing atrial fibrillation. The most common risk factor is hypertension but other factors such as other heart disease, obesity, diabetes, hyperthyroidism, chronic kidney disease, family history, heavy alcohol use, and pericardial fat, among others, have been found to be associated with increased risk of having AF[1,21-25]. One strongly associated cardiac lesion with AF is valvular disease, specifically mitral stenosis and mitral regurgitation which have been found to be associated with with a relative risk of AF as high as 2.42 (Table 1)[26].

Age, LA size, CHF, and hypertrophic cardiomyopathy (HCM) also stand out as particularly high-risk associations with AF[21,26,27]. There is also a general association with these conditions and ventricular diastolic dysfunction, and the link between diastolic dysfunction and AF has become better recognized recently[28]. Although associated with AF, these other clinical factors have not yet been associated with the primary development of atrial fibrosis by MRI.

Atrial function and ventricular dynamics

One correlate of atrial remodeling is atrial function, both passive and active. Below we present data on the relationship between atrial function and atrial fibrosis. However, any analysis of atrial dynamics cannot be considered thorough without recognizing the importance of the link between left ventricular

filling and left atrial emptying. Atrial emptying, like ventricular filling, happens in three parts under normal physiologic conditions. 1) An early passive phase that begins immediately after isovolumetric relaxation of the left ventricle when the mitral valve opens and blood flows from a full left atrium to an “empty” left ventricle. This flow of blood is very rapid. 2) A mid diastolic phase when blood fills both the left atrium and ventricle from the pulmonary veins while the mitral valve is open. The flow of blood through the valve is slow and this phase is also called the conduit phase. 3) A late, active phase caused by contraction of the left atrium which forces more blood into the left ventricle immediately prior to mitral valve closure and ventricular contraction. Figure 3 displays the volume of the LA during the cardiac cycle.

There are multiple well-established metrics for evaluating diastolic filling of the left ventricle on echocardiography. These include the peak filling rate (PFR) of blood flow through the mitral valve during early filling, the time from the beginning of diastole until this peak occurs (time to PFR), the estimated time from this peak until blood slows during mid diastole (deceleration time), ratios of initial filling velocity to tissue movement (E/e’) and late filling velocity (E/A) are just a few. Though well established for echocardiography, measures of diastolic function for cardiac MRI are relatively new and attempt to quantify surrogates of the echocardiographic measures because equivalent measures are challenging to achieve on MRI (Figure 4)[29]. Consider flow velocity through the mitral valve. While phase contrast imaging can be used to quantify flow through a plane that includes the valve, this plane would need to change in order the accommodate

movement of the mitral valve during ventricular filling. This challenge limits the utility of using this technique in clinical scanning, especially when an ultrasound is cheaper and better able to measure flow with Doppler. Additional measures of diastolic function on cardiac MRI are limited by temporal resolution or the use of special tissue tracking techniques that have to be applied at the time of image acquisition[29].

The surrogates of echocardiographic diastolic function used in cardiac MRI rest primarily upon changes in the volume of the left ventricle[30]. The ability of cardiac MRI to accurately define ventricular volumes, detailing papillary muscles and endocardial trabeculations, is one of the method's strengths (Figure 5). Although temporal resolution imposes some limitation on accuracy, ventricular filling rates can be estimated from changes in ventricular volume over time and be divided into the three phases mentioned earlier. Again, this is a surrogate for directly measured flow velocities for a few reasons. One is that velocity through the valve will be dependent on more than just the volume flowing through it and will be related to parameters such as pressure gradients and valve area. Also, this MRI approximation is a good surrogate only when aortic regurgitation is minimal or non-existent so that this volume does not contribute significantly to the end-diastolic volume. Regardless of their limitations, these measures of diastolic function, discussed in the methods and discussion, are used in the current study and the vast majority of studies, because they were the only ones available for the most of our subjects.

Describing diastolic dysfunction

Irrespective of the imaging modality used, combinations of these measures have also been used to identify different stages and degrees of diastolic dysfunction. From a physiological standpoint, diastolic dysfunction progresses from impaired myocyte relaxation to reduced ventricular wall compliance. Briefly, impaired relaxation leads to slower early filling rates with relatively greater contributions from left atrial contraction. As the dysfunction progresses, the ventricle begins to act like a stiffened spring, and after contraction, the unusually thickened myocardium rapidly springs open and fills quickly, early. Ventricular filling pressures are then high and relatively less blood enters the ventricle during the mid diastolic, “conduit” phase. Atrial contraction does little to contribute to ventricular end diastolic volume as it is pushing into a stiffened ventricle under higher pressure. These changes affect echocardiographic measures in well-established, predictable ways that generally allow for classification into grade 1, 2, or 3 diastolic dysfunction for a given subject. Classification of diastolic dysfunction based on the surrogate MRI metrics of diastolic dysfunction is new and less able to distinctly classify subjects into each of the three established grades[31]. Regardless of this issue, cardiac MRI studies have been able to show that increased left ventricular pressures, which can occur with diastolic dysfunction, do affect left atrial emptying dynamics[32]. This supports our hypothesis that diastolic dysfunction may also affect left atrial fibrosis.

Among subjects with AF: the additional effect of mitral regurgitation

Mitral regurgitation is a risk factor for the development of atrial fibrillation likely mediated by its effect on atrial remodelling, increased volume, and fibrosis development[9,10,33]. However, within AF subjects, the association of mitral regurgitation with LA LGE is not well described. In spite of knowledge of the role of mitral regurgitation in AF development, recent histopathology data of the left atrial appendage of AF patients suggest that LA fibrosis is less prevalent in subjects with mitral regurgitation compared to those with mitral stenosis[34]. Further, another data set with few subjects does not show a relationship between mitral regurgitation and LA LGE among AF patients[35]. We hypothesized that increasing MR would result in increased LA LGE and examined this relationship in a cohort with mitral regurgitation and AF.

Statement of Purpose/Aims

Despite its value in patients already found to have AF, patterns of LA LGE in patients without AF have remained largely unexamined until very recently[36]. Cochet el al found that, other than AF, LA LGE was associated with age and structural heart disease[36]. In the current study, we examined the relationship between LA LGE, particular clinical conditions, and measures of cardiac function (atrial and ventricular, active and passive) in a population of patients with and without AF. We hypothesized that patients with clinical risk factors of atrial fibrillation such has CHF, HCM, enlarged LA, and ventricular diastolic dysfunction would have increased LA LGE in addition to those with AF. We also

hypothesized that increased atrial fibrosis would reduce the active and passive emptying of the left atrium.

Methods

Patient Population and Clinical Data

This study was an IRB approved, retrospective review of all subjects imaged with a late enhancement cardiac MRI sequence at our institution from 2012 to 2014. Indications for imaging were diverse (Table 2) as this LGE sequence was acquired as an added component of standard cardiac MRI protocols. After initial identification of subjects in our PACS data-base, chart review of the electronic medical record was conducted to extract subjects' clinical information from physician notes. Additionally, routine quantitative data describing cardiac structure and function was obtained from the clinical imaging report including LV end-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (EF). Of the 304 subjects initially identified, those who had a prior sternotomy or catheter ablation of any type (28), or who were age 20 and younger (46), were excluded. An additional 93 subjects were excluded due to assessment of poor image quality (e.g. excessive motion artifact, poor contrast, or poor inversion time choice), resulting in a final study population of 137 subjects.

Cardiac Imaging and Measurements

Cardiac imaging was performed on Siemens 1.5T MR scanners at our institution (Aera, Siemens Healthcare, Erlangen Germany). The LA was imaged during mid

ventricular diastole using an ECG-triggered and navigator-gated, fat-saturated 3D gradient echo inversion recovery sequence, 15-25 minutes after administration of 0.2mmol/kg gadolinium contrast agent (Gadobutrol, Bayer Healthcare, Leverkusen, Germany). Voxel size was 1.32 x 1.32 x 3.0 mm^3 with interpolation to 0.66 x 0.66 x 1.5 mm^3. Additional scan parameters were: TR/TE/q= 5.3ms/2.1ms/15°. 25 views per segment were acquired, in a ky-centric order.

LGE in the LA was described by its subjective presence or absence in 18 locations (4 around each pulmonary vein, the posterior wall, and the inter-atrial septum), resulting in a semi-quantitative LGE score, which is scaled to 100 (Figure 1). Quantitative measurement of LGE volume was also performed using a threshold of 3.5 SDs above the mean blood pool. Inter and intra rater reliability of this method has shown to be good in other similar studies[36] and all LGE analysis was conducted by an experienced rater who was blinded to clinical data. The volume of segmented LGE enhancement was obtained using summation of segmented areas of enhancement in each axial slice (Figure 2).

Subjects were also imaged with cine steady state free precession two chamber and four chamber views, and with a short axis stack of the left ventricle from the apex to the base. Scan parameters include: Balanced SSFP cine with retrospective ecg-triggering, TR/TE/flip=3ms/1.5ms/60°, 30 cardiac phases. 1.4 x 1.4 x 8mm resolution. Measurements of the LA end-diastolic volume and LA

end-systolic volume were approximated by the biplane area-length method[37] (Figure 5b) and used to quantitate LA EF. An extension of this method was used to estimate the total volume of LA tissue at end-diastole with an assumed average left atrial wall thickness of 2.1mm[38] and the surface area of the LA modeled as a scalene ellipsoid. LA LGE volume as quantitated above was divided by total LA tissue volume to calculate an LA fibrosis percentage.

Assessment of active and passive atrial function.

In a subset of the first 42 consecutive subjects in the entire cohort who did not have AF, LA volume throughout the entire cardiac cycle was measured, also using the biplane method. Only the first 42 of 101 total non-AF subjects where used due to the time intensive nature of this method. Atrial emptying was divided into passive and active phases based on changes in slope of the time volume curve. The active and passive EF were then calculated (Figure 3)[39]. In the same subset, left ventricular volumes were also quantified using Simpson's method (summation of discs) across the cardiac cycle and used to construct a ventricular volume vs. time curve with a MATLAB (The Mathworks, Natick MA) spline fitting function. From this curve, a derivative curve was constructed and used to calculate peak filling rate, time to peak filling rate, and early to late filling rate ratio (E:A)[30] (Figure 4). Percent length of diastole to recover 60% of ventricular stroke volume (DVR) was calculated from the original volume vs time curve. Contours used to calculate LV volumes did not include the most basal

slice. These LV metrics of diastolic function were used to adjust for the well-known impact of diastolic function on passive LA function.

Assessment of mitral regurgitant fraction (MRF)

In a subset that included all subjects with AF (n=35; one AF subject lacked a phase contrast sequence), mitral regurgitation was quantified as a fraction of ventricular stroke volume. To calculate this value, ventricular endocardial borders were contoured at end systole and end diastole using a semi-automatic threshold detection technique that excluded ventricular trabeculations and papillary muscles from volume measurements. Because of the nature of this method for determining mitral regurgitant fraction, it was essential to include the basal slices of the heart when calculating these volumes. Similar to the above, Simpson's method was used to calculate the ventricular volumes from these contours and the difference between these volumes was the stroke volume. Forward flow through the aorta was quantified using phase contrast imaging during ventricular systole. By process of exclusion in normal cardiac anatomy, ventricular stroke volume that does not flow forward through the aorta must be flowing retrograde through the mitral valve into the LA. As such, the mitral regurgitant volume is the ventricular stroke volume minus the aortic forward flow, and was represented as a percentage of the ventricular stroke volume.

All image post processing was done using Circle Cardiovascular Imaging software v4.2 (Calgary, CA).

Data Analyses

In this retrospective review, the clinical data gathered included sex, weight, height, smoking status, and other attributes of past medical history with specific attention to cardiovascular disease and risk factors. Not all study data was available for all subjects, and subjects were included in each analysis only when pertinent data were available in the record (Table 3). An incomplete record resulted from some patients who were referred to this institution for imaging by providers outside of the network; there is no chart in our EMR for such patients. Finally a reference group was identified from the entire 137 member cohort using a predetermined set of criteria: No structural or myopathic cardiac disease, no atrial fibrillation, no more than mild mitral regurgitation, no diagnosed coronary disease if subject has had a cardiac catheterization, LV EF >45%, and LV EDV index <90 ml/m^2. Twenty-three reference subjects fit these criteria. These were usually subjects referred for work-up of suspected arrhythmogenic RV cardiomyopathy or cardiac sarcoidosis whose MRI was negative for signs of such pathology.

Statistics

In describing the relationship between LA LGE with clinical and cardiac variables, LGE was analyzed as a percentage of estimated LA tissue volume and as a semi-quantitative LGE score. Analysis using both metrics of LGE was done to determine whether there are differences in the ability of each to find trends, as each is different in its quantification of different patterns of LGE (see discussion). Student's t-tests were used to compare LGE tissue percentages among subjects

with vs. without varying conditions while Mann-Whitney tests were used for similar comparison of LGE scores. Pearson correlations were used to describe the relationship between continuous variables such as age, LA volume, atrial and ventricular emptying and filling measures, and LGE tissue percentage while Spearman correlations were used for similar analyses of LGE score. A least squares multivariate regression was used to describe the relationships of clinical conditions with the percentage of LA LGE. Clinical conditions in the model were chosen based on a threshold of $p < 0.1$ in the univariate analysis. Separately, multivariate adjustment for ventricular filling dynamics was made to describe the relationship among LA LGE tissue percentage and atrial passive emptying. Similar analysis of ventricular filling and atrial emptying was conducted using LGE score quartiles. Square root or logarithmic transformations were used to allow for parametric analysis of otherwise non-normally distributed continuous data. All statistical analyses were performed using JMP v11 (SAS Institute, Cary NC).

Contributions of colleagues

Dana Peters: Provided initial direction of research inquiry, provided data from pilot study, quantified LGE score and LGE tissue percentage, provided ongoing feedback regarding analyses and future directions

Lauren Baldassarre: provided continuing feedback on direction of the project, verified phase contrast forward flow measures and ventricular contours for calculating stroke volumes and mitral regurgitant fractions.

Karl Grunseich: Conducted all other aspects of the project including: expanding scope of the research question, identification of new subjects, clinical chart review, imaging report review, contouring of the atrial and ventricular borders of subjects in each respective analysis, post-processing of atrial and ventricular volume-time data, all statistical analysis.

Results

Measurement of LA LGE: Quantitative vs. Semi-quantitative.

Our two measurements of LA LGE are not equivalent to each other. LA LGE scores are more representative of the distribution of fibrosis across the LA; they indicate the percentage of 18 different possible regions that show enhancement. Left atrial fibrosis percentage is a measurement of volume of enhanced tissue relative to total atrial tissue. This measure may represent a single large area of enhancement in a way that is similar to many small, scattered regions of enhancement. Although these measurements indicated different aspects of the enhancement pattern, they are strongly correlated to each other ($r_s = 0.699$, $P < 0.001$ Figure 6). The fully quantitative method required ~5 minutes of analysis, vs. <1 minute for the semi-quantitative method.

Association with clinical conditions

The study population was 59% male, with a mean age 51.3 (SD 13.8), a mean of BMI 28.5 (SD 5.9), and a diverse distribution of cardiovascular disease and risk factors (Table 3).

LGE percentage

There is a moderate but significant correlation between age and percentage of atrial tissue enhancement ($r = 0.359$ $p < 0.001$). In univariate analysis of each clinical factor considered within the entire cohort, only subjects with CHF or any mitral regurgitation had greater percentage of LA tissue enhancement than those without those conditions (Table 4a). In a multivariate regression including HCM, CHF, AF and mitral regurgitation, HCM and CHF were independently associated with increased LA LGE (Table 4b). Continuous variables of age and LA EF were not included in the multivariate analysis as they are closely associated with CHF and AF, causing concerns of multicollinearity. When compared to the relatively healthy reference subjects, those with HCM, CHF, greater than mild mitral regurgitation and AF all had significantly higher LA LGE tissue percentages (Table 5, Figure 2). We did not find any relationships with risk factors of cardiovascular disease, such as hypertension, obesity, or diabetes, and LA LGE.

LGE Score

There is a weak, non-significant correlation between age and LGE score ($r_s = 0.147$ $p = 0.087$). In univariate analysis of each clinical factor considered within the entire cohort, only subjects with CHF or HCM had greater percentage of LA tissue enhancement than those without those conditions (Table 6). A multivariate regression including HCM and CHF had a statistically significant lack of fit test ($p = 0.042$). Continuous variables of LA EF or LA volumes were not included in the multivariate analysis as they are closely associated with CHF, causing concerns of multicollinearity. When compared to the relatively healthy reference subjects,

those with HCM, CHF, greater than mild mitral regurgitation and AF all had significantly higher LA LGE scores (Table 5, Figure 2). We did not find any relationships with risk factors of cardiovascular disease, such as hypertension, obesity, or diabetes, and LA LGE score.

Association with atrial size and function

LGE percentage

Across all subjects, there was a weak to moderate but significant correlation between both maximum and minimum LA volume and LA LGE percentage (Figure 7,Table 7). These relationships were also similar for subjects with and without atrial fibrillation (Table 7). Additionally, there was a moderate correlation between overall LA ejection fraction and LA LGE percentage that was similar in a subset of subjects with and without atrial fibrillation (Table 7).

LGE Score

Across all subjects, there was a weak to moderate but significant correlation between both maximum and minimum LA volume and LA LGE score (Figure 7, Table 7). These relationships were also similar for subjects with and without atrial fibrillation, although statistical significance was not achieved from AF subjects (Table 7). Additionally, there was a moderate correlation between overall LA ejection fraction and LA LGE score that was similar in a subset of subjects with and without atrial fibrillation (Table 7).

Association with ventricular functions

LGE percentage

In a subset of 42 subjects without AF, there was no direct relationship between peak filling rate, time to peak filling rate, and proportion of diastole to 60% diastolic volume recovery with LA LGE tissue percentage (r = -0.168 p = 0.288, r = 0.036 p = 0.820, r = 0.139 p = 0.380 respectively). There were strong correlations between both ventricular peak filling rate and time to peak filling rate with passive atrial ejection fraction (r = 0.723 p < 0.001; r = -0.502 p < 0.001 respectively). Increasing LA LGE tissue percentage and peak filling rate were independently associated with decreasing and increasing passive LA EF respectively, while time to peak filling rate was not (Table 8). There was also a lower active atrial ejection fraction in subjects with increasing LA LGE tissue percent (r = -0.438 p = 0.004).

There was no relationship between LV EF and LA LGE (r = 0.071 p=0.418). However, among patients with CHF and preserved EF (EF>45%) there was greater LA LGE percentage compared to those with lower LV EF (p = 0.032, Figure 8).

LGE Score

There was no direct relationship between LGE score and markers of diastolic dysfunction (including PFR, time to PFR, or proportion of diastole to 60% diastolic volume recovery; r_s = 0.072 p = 0.653, r_s = -0.015 p = 0.925, r_s = -0.067 p = 0.675 respectively). After adjustment for the relationship of PFR and time to PFR with passive atrial EF, those subjects in the highest LA LGE quartile had lower passive atrial ejection fraction when compared to those in the lower two LA

LGE quartiles (p=0.020; Figure 9). In multivariate analysis, PFR (p < 0.001) but not time to PFR (p = 0.063) was independently associated with passive LA EF. There was also a lower active atrial ejection fraction in subjects in the highest compared to the lowest LA LGE quartile (p = 0.047).

There was no relationship between LV EF and LA LGE score (r_s = -0.032 p = 0.711). Among patients with CHF and preserved EF (EF>45%) there was no difference in LA LGE score compared to those with lower LV EF (p = 0.085).

Association of LGE with mitral regurgitation in subjects with AF

In a sub-study of 35 AF subjects, we investigated the hypothesis that AF patients have greater remodeling in the presence of mitral regurgitation (MR). Subject characteristics were 69% male, mean age 56.4±10.1, mean BMI 30.0 ±5.3, 51% hypertensive, 20% congestive heart failure, and 14% diabetic. MR was visualized in 60% of subjects (16 mild, 3 moderate, 2 not described). The presence of visual MR was associated with increased maximum LA volume (p = 0.001) and increased MRF (p = 0.022, Figure 10). Maximum LA volume was poorly associated with quantitative MRF (r = 0.232, p = 0.186).

LGE percentage

The presence of visual MR was not associated with higher LA LGE percentage (p = 0.307). Maximum LA volume was weakly and not significantly associated with LA LGE percentage (r = 0.221, p = 0.201). Direct association between MRF and LA LGE percentage (r = 0.129 p = 0.467) was not observed. Adjustment for

LA volume did not impact the relationship between MRF and LA LGE percentage (r_p = 0.108 p = 0.590).

LGE Score

The presence of visual MR was not associated with higher LA LGE score (p = 0.672). Maximum LA volume was not associated with LA LGE score (r_s = 0.146, p = 0.402). Direct association between MRF and LA LGE score (r_s = 0.140 p = 0.430) was also not observed. After adjustment for LA volume, increased MRF was not correlated with LA LGE score (r_p = 0.047 p = 0.803).

Discussion

Quantitative vs. semi-quantitative assessments

The quantification of LA LGE remains a relatively controversial area within the field of cardiac MRI. The current "gold standard" involves contouring the endocardial and epicardial border of the atrial tissue in each axial reconstructed slice. The enhancement threshold above the blood pool is then applied to the contoured atrial tissue, and both the enhanced and unenhanced areas are summed across all slices to calculate the fraction of atrial tissue that is enhanced. This process is incredibly time intensive and, if the service is provided by a third party, expensive. In this study we used two different methods of LGE quantification of varying simplicity. The tissue percentage we calculated in this study approximates the gold standard by estimating the volume of the total atrial tissue, which serves as a denominator for the fraction of enhanced tissue; the

volume of the enhanced tissue is calculated directly. This measure does not distinguish well between a single large area of fibrosis and several smaller, scattered areas of fibrosis, but is a relatively robust indicator of total atrial fibrosis burden. The LGE score we used is more subjective, as it is based on an experienced rater's interpretation of enhancement in 18 pre-determined regions of the LA. It also is a better indicator of the overall spacial extent of LA LGE, but may understate one or two large but confined areas of LGE. This score assessment can be made relatively quickly, easily, and without the expense of external proprietary processing. The ultimate goal of this research is for the LA LGE protocol to be used clinically if the sequence is found to add value to patient prognosis and management. These features of the LGE score make it an attractive measure in the clinical arena.

We found there to be a strong correlation between the two LA LGE measures used in this study. This indicates that subjects with an increased amount of LA LGE tend to have that LGE be distributed broadly throughout the LA instead of confined to one or two regions. This agreement also gives support to the use of the LGE score as an easier method of LGE quantification. However, there were some differences in the conditions and functional metrics each measure of LGE was associated with. On univariate analysis for example, LGE score was significantly greater in subjects with HCM while LGE percentage was not. Also, LGE percentage was greater in subjects with mitral regurgitation and marginally with AF while LGE score was not. This type of discrepancy may indicate

differences in how atrial fibrosis is distributed in the LA among these conditions. For example, subjects with mitral regurgitation may not have a wider distribution of LGE in the LA than those without, but do have more LGE in the regions where they do have enhancement. Also, subjects with HCM do have greatly elevated LGE scores that indicated the atrial fibrosis is wide-spread, rather than confined to one area as could be interpreted from the LGE percentage.

It is important however, not to overlook how the subjective nature of the LGE score and the multitude of statistical tests done on this data set, which may increase the odds of false positive results. A decision was made not to use a Bonferroni correction in these analyses because this would severely limit our ability to find any differences in this relatively small population in a largely hypothesis generating study meant to guide future research. In order to avoid confusion for the remainder of the discussion, results referenced will be from the slightly more quantitative and robust LGE percentage.

Atrial LGE, Clinical Conditions, and Cardiac Structure

The main finding of this study is an increased extent of atrial LGE in patients with CHF, HCM, mitral regurgitation, and/or AF compared with the control group. In pathology studies, many of these cardiac diseases have been individually associated with increased atrial fibrosis. For example, LA fibrosis and electrophysiological remodeling have been demonstrated to provide a substrate for the development and persistence of AF[11]. Heart failure without AF is also

associated with atrial fibrosis by pathology[40], and it is known that CHF is associated with increased incidence of AF with prevalence as high as 44%[41] in this group of patients. Previous studies of atrial fibrosis by LA LGE have nearly exclusively examined patients with AF. A recent study did find a correlation of LGE with structural heart disease in general but did not focus on specific disease states[36]. In this study, we demonstrated that atrial fibrosis can be detected by LA LGE MRI in subjects without AF who have CHF, HCM, or mitral regurgitation, a finding which could have implications for future management of patients with these conditions.

Atrial LGE is only mildly associated with maximum LA size, but moderately associated with minimum LA size and LA EF in this study. Prior studies have shown that minimum atrial volume is a stronger correlate with AF development, adverse cardiovascular events, and NT-proBNP, compared with maximum volume[42-44]. Similarly, minimum atrial volume is more strongly correlated with atrial LGE in this study.

Although a relationship with atrial volume exists, LA LGE is not simply a surrogate for LA volume. Factors such as atrial size have been shown to be tied with outcomes in patients with heart failure[45] and LA LGE could provide additional new prognostic or decision guiding data in the management of these patients that LA size alone does not. For example, within AF subjects Daccarett et al.[18] demonstrated increased predictive value of LA LGE beyond the $CHADS_2$

score for determining stroke risk. Analogously, the risk of developing AF in CHF patients could include LA LGE as a valuable predictor. Also, ACE inhibitors can reduce atrial fibrosis and mitigate the risk of AF development[46]. The presence of LA LGE in a patient without AF could be a factor in selecting patients who would benefit from initiating these drugs or in dose adjustment for patients who are already taking them. These possible prognostic and clinical uses for measuring LA LGE need further study.

Although there were a small number of subjects with HCM, those subjects had substantially higher LA LGE percentages compared to others in the reference group. To date, studies of LGE in hypertrophic cardiomyopathy have primarily been limited to ventricular LGE. Such studies have shown ventricular LGE to be related to AF[47] and diastolic dysfunction[48,49]. HCM in general has a strong relationship with atrial fibrillation and heart failure, with increased LA size and decreased LA function associated with particularly high AF risk[27,50]and worse heart failure symptoms[51]. Measurement of LA LGE in this population of patients could provide similar clinical value as for CHF regarding risk assessment, management, and prognostic value. As with CHF, further study is needed in a larger population of these patients to identify risks or prognosis independently associated with LA LGE.

Cochet et al[36] found age to be an independent predictor of LA LGE. We also found that increasing age was associated with increased LA LGE, but this

association was weaker. Since conditions associated with increased LA LGE (CHF, AF) are also associated with increasing age, we were not able to establish an independent effect of age due to concerns of multicollinearity. Additionally, we were not able to establish an independent association of AF with LA LGE, although LGE was greater in the AF group than the healthy reference group. This may have been due to our relatively smaller cohort compared to other studies or due to a cohort with more paroxysmal vs. persistent AF patients, as persistent AF has been associated with greater LA LGE[19]. Our study also did not demonstrate any direct relationship with other cardiovascular risk factors (e.g. hypertension or hyperlipidemia) or subject sex with the burden of LA fibrosis by LGE. These conditions may not be strongly associated with fibrosis on their own, or such an association may not be able to be detected by LA LGE in a study of this size and type.

Atrial LGE and Atrio-Ventricular Dynamics

The recognition of diastolic dysfunction as a potential risk factor for AF is gaining strength[28]. Increased LA LGE in AF, HCM and CHF –all associated with diastolic dysfunction—suggests that there may be a more general association of left ventricular dynamics and LA LGE, especially as both the current and other studies[51] have demonstrated close association between ventricular function and atrial filling and emptying dynamics. Across a diverse subset of patients without AF, we demonstrated that LA LGE was associated with reduced active and passive atrial ejection fractions, similar to what has been found in AF patients[20].

Additionally, in the study as a whole, there is an association of decreased overall LA ejection fraction with increased LA LGE. Together these results suggest LA LGE detected fibrosis is a marker of poor atrial function. In patients with altered systolic or diastolic ventricular function, it may be development of atrial fibrosis that further decreases the atrial contribution to overall cardiac function, potentially contributing to patients' heart failure symptoms. Our finding of increased LA LGE in patients with heart failure but preserved LV EF supports this hypothesis.

Lack of correlation between diastolic function and atrial LGE

What remains poorly demonstrated is whether ventricular dysfunction itself can be directly related to left atrial fibrosis. In the current study, we did not find a direct correlation between ventricular diastolic filling parameters and LA LGE, although we were limited by a smaller sample size and the retrospective nature of this study. Initially, we had intended to establish the grade of diastolic dysfunction for the subjects for whom we calculated the diastolic filling parameters. However, this was not possible because we lacked the ability to distinguish between normal diastolic filling and grade 2 or "pseudonormal" diastolic filling. This problem arises because of how the measures of ventricular filling change as diastolic dysfunction progresses. With impaired relaxation there is an initial decrease in early peak filling rate and an increase in time to peak filling rate. As diastolic dysfunction progresses and the ventricle stiffens, this change reverses and the peak filling rate increases and time to peak filling rate decreases. Because of this trend, there is a time in the progression of diastolic

dysfunction when these numbers appear normal. In echocardiography, there are well-established parameters based on measures of tissue movement that can distinguish true from pseudo normal. Unfortunately, MRI currently lacks such distinguishing measures as even the measures of diastolic dysfunction unique to MRI, e.g. proportion of diastole to 60% diastolic volume recovery, change in a way similar to time to peak filling rate. Once a reliable distinguishing measure is established that can be applied to previously acquired images for MRI, it will be useful to revisit this subject population and stratify the grade of diastolic dysfunction and look for patterns of LA LGE.

MRF is not correlated with LGE among AF subjects

In examining the subjects with AF in our study, we did not find any measures of mitral regurgitation to be associated with LA LGE score or tissue percentage. It is well established that many patients with AF have LA LGE, and our intent was to find whether mitral regurgitation moderates or amplifies the quantity of LA LGE in these AF subjects. There is a growing body of literature of correlates of LA LGE in AF studies much larger than ours which have found atrial functional measures, time in AF, and pattern of AF to be associated with LGE quantity[19,20]. Given that these factors are known to influence the amount of LGE in the LA, it is reasonable for us not to find an association of mitral regurgitation without first being able to adjust for these other factors (we lacked adequate data in this retrospective analysis). This would especially be true if the effect of mitral

regurgitation is relatively weak, as might be the case in our data set as most subjects had mild, if any, regurgitation.

Conclusion

In assessments of LA LGE in a diverse population, we found that extent of LGE correlates with the presence of CHF, AF, HCM, mitral regurgitation, and age, though independence could be established only for CHF and HCM. We also found moderate relationships between LA LGE and LA volume, LA active EF, and LA passive EF, after accounting for ventricular diastolic function. Each of these findings of association of LA LGE with cardiac conditions and functional metrics lays the groundwork for further inquiry into the utility of measuring LA LGE in subjects beyond those with AF.

In particular, a prospective study following patients with CHF or HCM with initial and follow-up LGE images and quantification could be fruitful, especially if patients were also followed with periodic holter monitoring to document development of atrial fibrillation. Such a study could determine variables that lead to greater progression of LGE burden and detect whether LGE burden is related to risk of AF. An additional study could also include an analysis to examine whether patients' medications, such as ACE inhibitors, influence LGE burden. With the results of this study, the need to further evaluate the value of LA LGE certainly seem worthy of pursuit.

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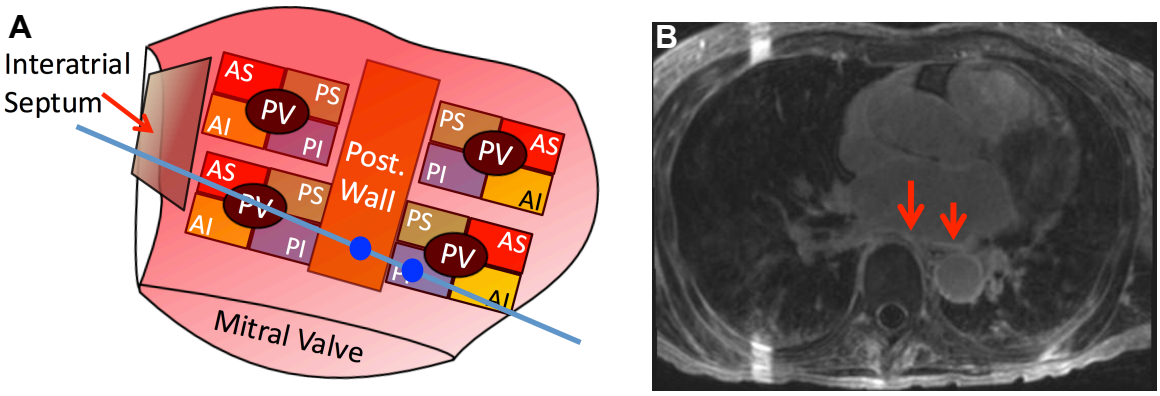

Figure 1. (A) Schematic of 18 regions in the LA used to quantify the presence of LA LGE included Anterior Superior (AS), Posterior Superior (PS), Anterior Inferior (AI), and Posterior Inferior (PI) regions around each pulmonary vein in addition to the posterior wall and interatrial septum. (B) Sample LGE image indicating two regions of enhancement (red arrows). Corresponding axial slice and enhanced regions indicated in A. Without enhancement in other planes, would have 2/18 segments or a score of 11 scaled to 100.

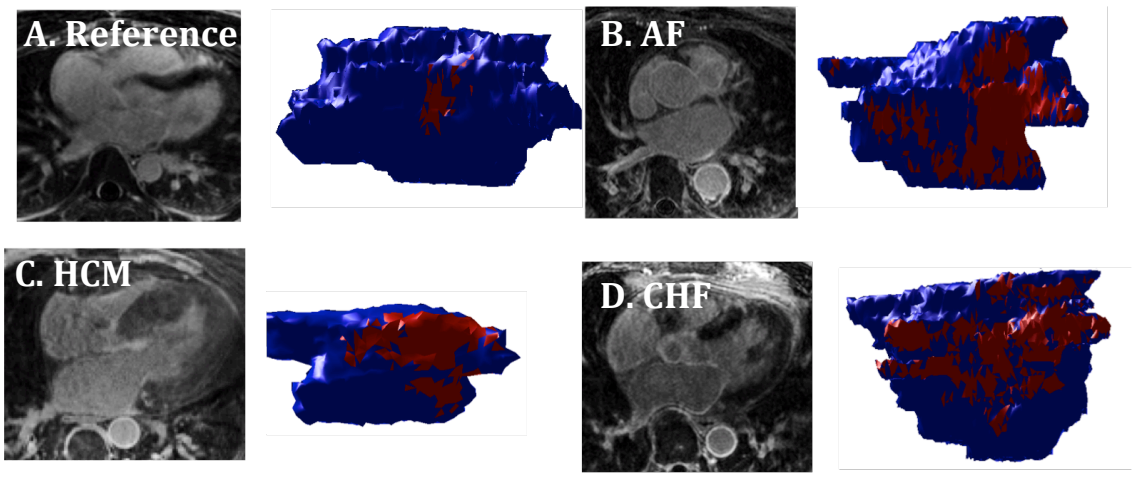

Figure 2. Four subjects with LA LGE, showing a single slice, and the 3D rendering of LGE (red) and normal tissue (blue). Subject A is a relatively healthy reference subject while subjects B, C, and D have atrial fibrillation, hypertrophic cardiomyopathy, and congestive heart failure, respectively.

Table 1. Independent Risk Factors for New Onset of Atrial Fibrillation in Older Adults (adapted from Psaty et al. Circulation 1997. 96:7 2455-61)

Variable	**RR**	**95% CI**
Alcohol, drinks/wk	0.96	0.93-0.99
Systolic BP, 10 mm Hg	1.11	1.05-1.18
Height, cm	1.03	1.02-1.05
Cholesterol, mmol/L	0.86	0.76 -0.98
Age, y	1.05	1.03-1.08
Glucose, mmol/L	1.08	1.03-1.13
Valve disease	2.42	1.62-3.60
β-Blockers	0.61	0.41-0.91
Diuretics	1.51	1.17-1.97
Coronary disease	1.48	1.13-1.95
Cardiac injury score	1.01	1.00-1.02
FEV_1, L	0.75	0.59 -0.94
Left atrial size, cm	1.74	1.44-2.11
Black race	0.47	0.22-1.01

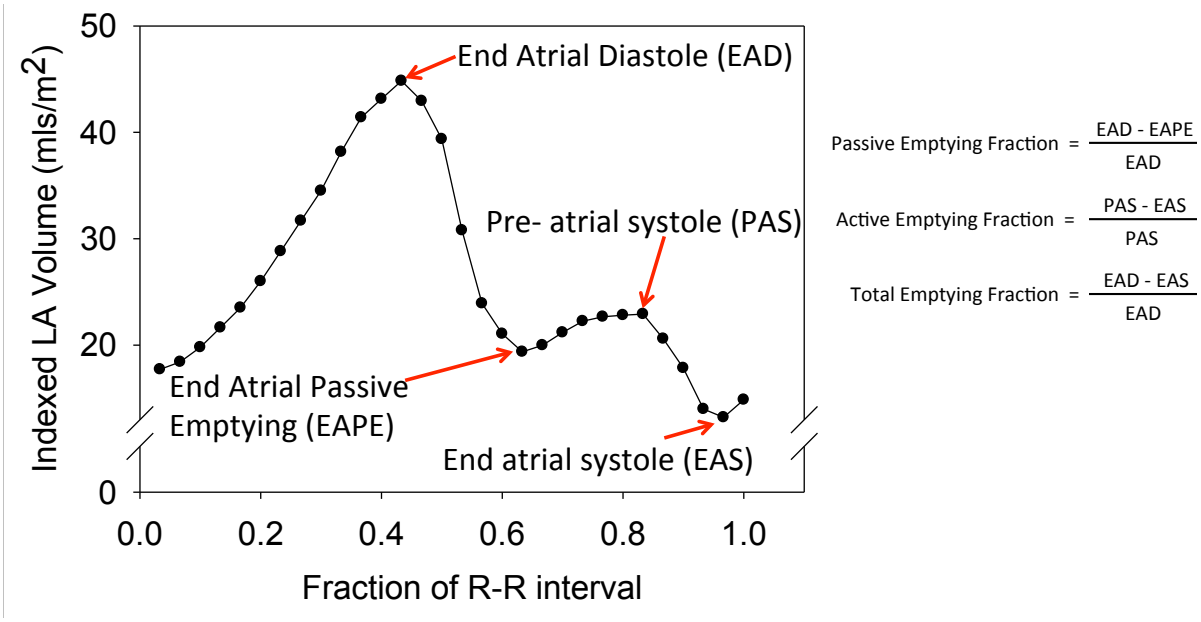

Figure 3. Representative curve of LA volume during the cardiac cycle with formulas used to quantify atrial functions.

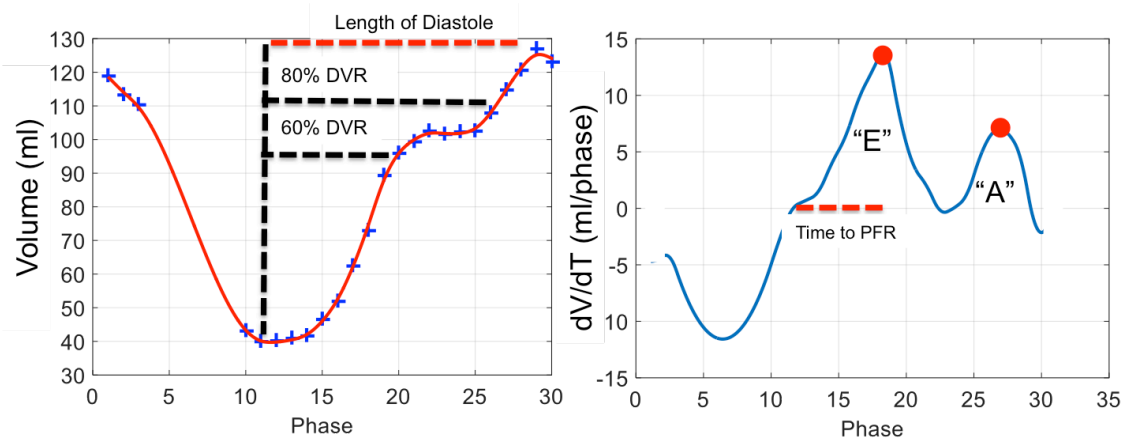

Figure 4. Representative curve of left ventricular volume (left) and its derivative (right) during 30 phases (time points) of the cardiac cycle with measures of diastolic function indicated. Diastolic volume recovery (DVR) is the proportion of diastole required for the ventricular volume to return to X% of the end diastolic volume. The "E" peak is the early peak filling rate (PFR), the "A" peak is the filling rate during atrial systole.

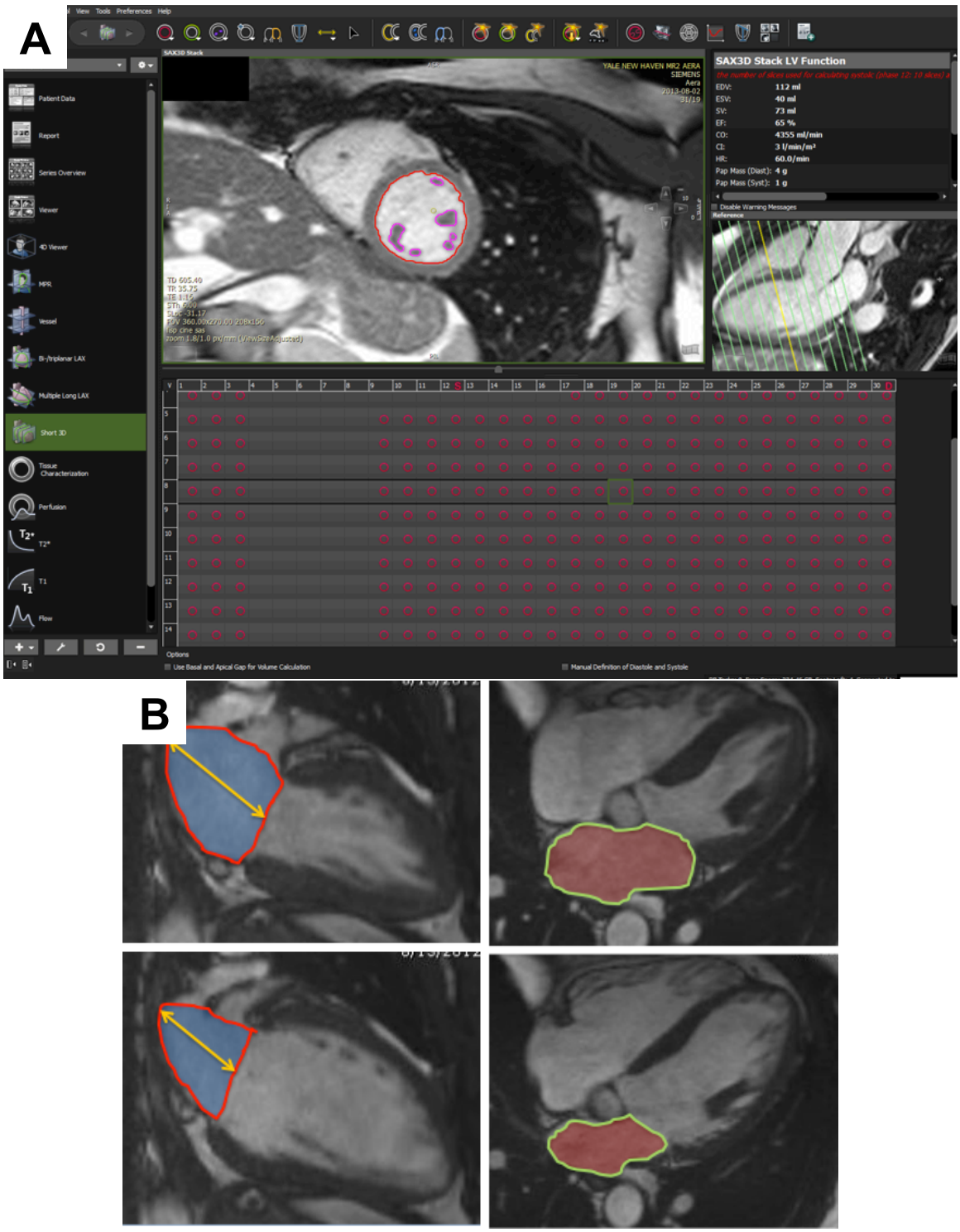

Figure 5. Screen capture of circle cardiovascular imaging software as used for post processing to (A) determine left ventricular volumes over the cardiac cycle and (B) estimate maximum (upper images) and minimum (lower images) atrial volumes. Note the clear distinction of the endocardial border (red) and papillary muscles (purple) in A. In B, the formula used to estimate volume is Vol = 0.001 x (0.85 x 2 chamber atrial area (at left) x 4 chamber atrial area (at right)/ 2 chamber length (yellow arrow).

Table 2. Imaging Indications

Indication	N
Cardiomyopathy	
Hypertrophic	9
Sarcoidosis/Infiltrative	39
Arrhythmogenic RV	26
General/Other	20
Atrial Fibrillation	29
Structural Disease	11
Myo/pericarditis	7
Mitral Regurgitation	4
Hemochromatosis	2
Other	12

Table 3. Population Characteristics (N= 137)

	Mean (s.d.) N (%)	# Subjects Missing
Age	51.3 (13.8)	0
BMI	28.5 (5.9)	10
Gender		
male	81 (59%)	0
female	56 (41%)	0
Atherosclerosis Risk Factors		
Tobacco Use	42 (37%)	23
Hyperlipidemia	53 (47%)	24
Hypertension	61 (48%)	11
Diabetes	14 (11%)	12
Selected Cardiac Disease		
Hypertrophic Cardiomyopathy	6 (4%)	0
Congestive Heart Failure	19 (14%)	4
Atrial Fibrillation	36 (28%)	7
Mitral Regurgitation	52 (38%)	0
Medication Usage*		
Beta-Blocker	48 (38%)	9
Calcium Channel Blocker	18 (14%)	9
ACE-Inhibitor	30 (23%)	9
Aspirin	45 (35%)	9
Statin	35 (27%)	9
Anti-arrhythmetic	17 (13%)	9

* at time of imaging
% considering only patients for whom data was available

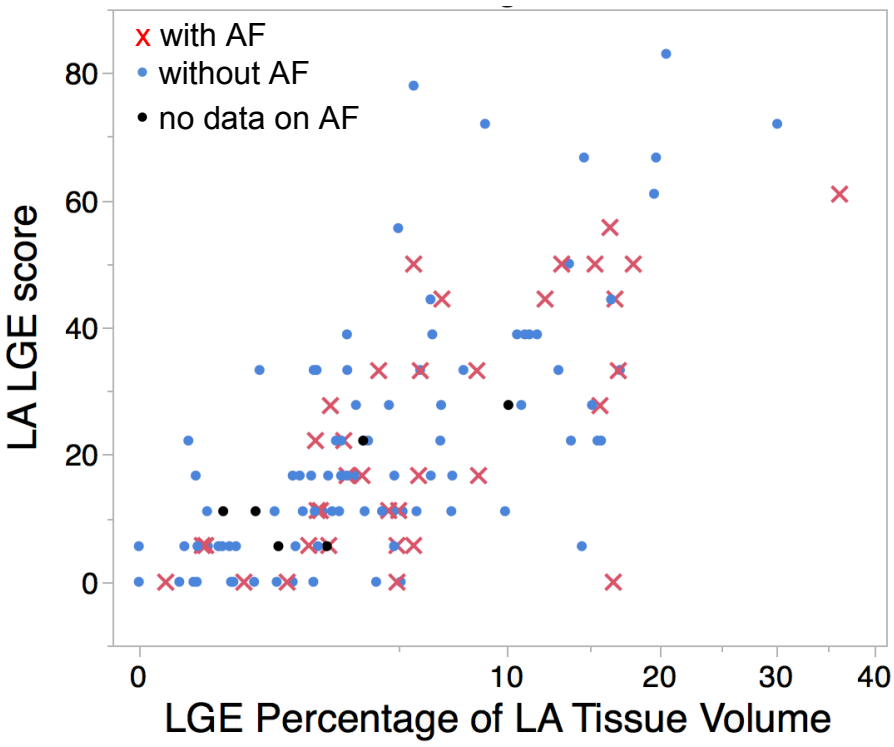

Figure 6. The quantitative LGE percentage of LA tissue volume is strongly correlated to subjective, semi-quantitative LA LGE score (r_s = 0.699 $p < 0.001$).

Table 4a. Conditions and association with LA LGE tissue percentage. Data are means (+SE), p value for t-test comparing subjects with (+) and without (-) a condition or characteristic.

		Overall		AF		without AF	
Condition		LGE %	p	LGE %	p	LGE %	p
Obesity	+ -	4.2 (0.6) 4.8 (0.7)	0.51	4.6 (1.0) 7.7 (2.1)	0.14	4.1 (0.8) 4.2 (0.7)	0.92
Gender	male female	4.4 (0.6) 4.6 (0.8)	0.83	4.8 (0.8) 9.4 (3.5)	0.14	4.2 (0.8) 3.7 (0.6)	0.65
Atherosclerosis Risk Factors							
Tobacco Use	+ -	4.3 (0.9) 5.0 (0.7)	0.47	4.9 (1.6) 6.6 (1.4)	0.41	4.1 (1.0) 4.3 (0.7)	0.9
Hyperlipidemia	+ -	4.3 (0.7) 5.4 (0.9)	0.28	4.1 (1.1) 8.0 (1.8)	0.06	4.3 (0.8) 4.3 (0.9)	0.97
Hypertension	+ -	5.1 (0.8) 4.1 (0.7)	0.34	5.4 (1.6) 7.0 (1.5)	0.45	5.0 (0.9) 3.5 (0.8)	0.19
Diabetes	+ -	5.6 (1.5) 4.4 (0.5)	0.44	7.4 (2.5) 5.9 (1.2)	0.58	4.7 (2.0) 4.1 (0.6)	0.72
Selected Cardiac Disease							
Hypertrophic Cardiomyopathy	+ -	10.5 (3.9) 4.2 (0.4)	0.09	N/A 6.1 (1.1)	N/A	10.5 (3.9) 3.7 (0.5)	0.06
Congestive Heart Failure	+ -	9.5 (1.6) 3.8 (0.5)	**<0.01**	10.1 (2.7) 5.3 (1.1)	0.08	9.1 (2.1) 3.4 (0.5)	**<0.01**
Atrial Fibrillation	+ -	6.1 (1.1) 4.0 (0.5)	0.06	N/A N/A	N/A	N/A N/A	N/A
Mitral Regurgitation	+ -	5.9 (0.9) 3.6 (0.5)	**0.02**	7.0 (1.8) 4.9 (1.1)	0.28	5.6 (1.1) 3.4 (0.6)	0.06

Table 4b. Multivariate analysis of factors associated with LA LGE

	Standardized β	p
Hypertrophic Cardiomyopathy	0.209	**0.013**
Congestive Heart Failure	0.274	**0.002**
Atrial Fibrillation	0.151	0.081
Mitral Regurgitation	0.093	0.297
Model r^2	0.173	**<0.001**

Table 5. Median (IQ range) for LGE Score and Mean (+SE) for LA LGE percentage of tissue volume for selected cardiac disease and comparison to reference group (Mann-Whitney test or t-test).

	LA LGE Score	p	LGE % of LA Tissue	p
Reference	11 (0-17)		2.1 (0.6)	
Selected Cardiac Disease				
Hypertrophic Cardiomyopathy	61 (38-74)	**<0.001**	10.5 (3.9)	**0.021**
Congestive Heart Failure	33 (22-44)	**<0.001**	9.5 (1.6)	**<0.001**
Atrial Fibrillation	17 (6-42)	**0.013**	6.1 (1.1)	**0.001**
Mitral Regurgitation	17 (6-33)	**<0.001**	7.9 (2.8)	**0.018**

note: reference group includes subjects with mild or no detectable mitral regurgitation

Table 6. Conditions and association with LA LGE Score. Data are median (interquartile range), p value for Mann-Whitney test comparing subjects with (+) and without (-) a condition or characteristic.

		Overall		AF		without AF	
Condition		LGE Score	p	LGE Score	p	LGE Score	p
Obesity	+ -	11 (6-28) 17 (6-33)	0.35	17 (6-33) 28 (6-46)	0.30	11 (6-28) 17 (6-33)	0.57
Gender	male female	17 (6-33) 17 (6-32)	0.76	17 (8-39) 17 (0-44)	0.63	11 (6-33) 17 (11-28)	0.49
Atherosclerosis Risk Factors							
Tobacco Use	+ -	11 (4-29) 17 (7-33)	0.24	11 (4-32) 19 (10-44)	0.27	11 (1-32) 17 (6-33)	0.51
Hyperlipidemia	+ -	11 (6-28) 17 (6-33)	0.44	17 (6-33) 28 (1-44)	0.70	11 (6-28) 17 (6-33)	0.52
Hypertension	+ -	17 (6-28) 17 (6-33)	0.71	17 (6-33) 28 (11-44)	0.20	17 (6-28) 11 (6-33)	0.87
Diabetes	+ -	11 (6-22) 17 (6-33)	0.65	17 (8-36) 17 (6-44)	0.96	11 (6-17) 17 (6-33)	0.44
Selected Cardiac Disease							
Hypertrophic Cardiomyopathy	+ -	61 (38-74) 17 (6-33)	**<0.01**	N/A 17 (6-42)	N/A	61 (38-74) 17 (6-28)	**<0.01**
Congestive Heart Failure	+ -	33 (22-44) 14 (6-28)	**<0.01**	33 (22-44) 11 (6-33)	**0.05**	36 (15-43) 17 (6-28)	**<0.01**
Atrial Fibrillation	+ -	17 (6-42) 17 (6-33)	0.57	N/A N/A	N/A	N/A N/A	N/A
Mitral Regurgitation	+ -	19 (6-33) 17 (6-33)	0.32	22 (6-44) 17 (6-33)	0.77	22 (11-33) 17 (6-33)	0.27

Figure 7. Associations of LA volumes and ejection fraction with measures of LA LGE. See Table 7 for correlations. x , --- with AF
• , — without AF

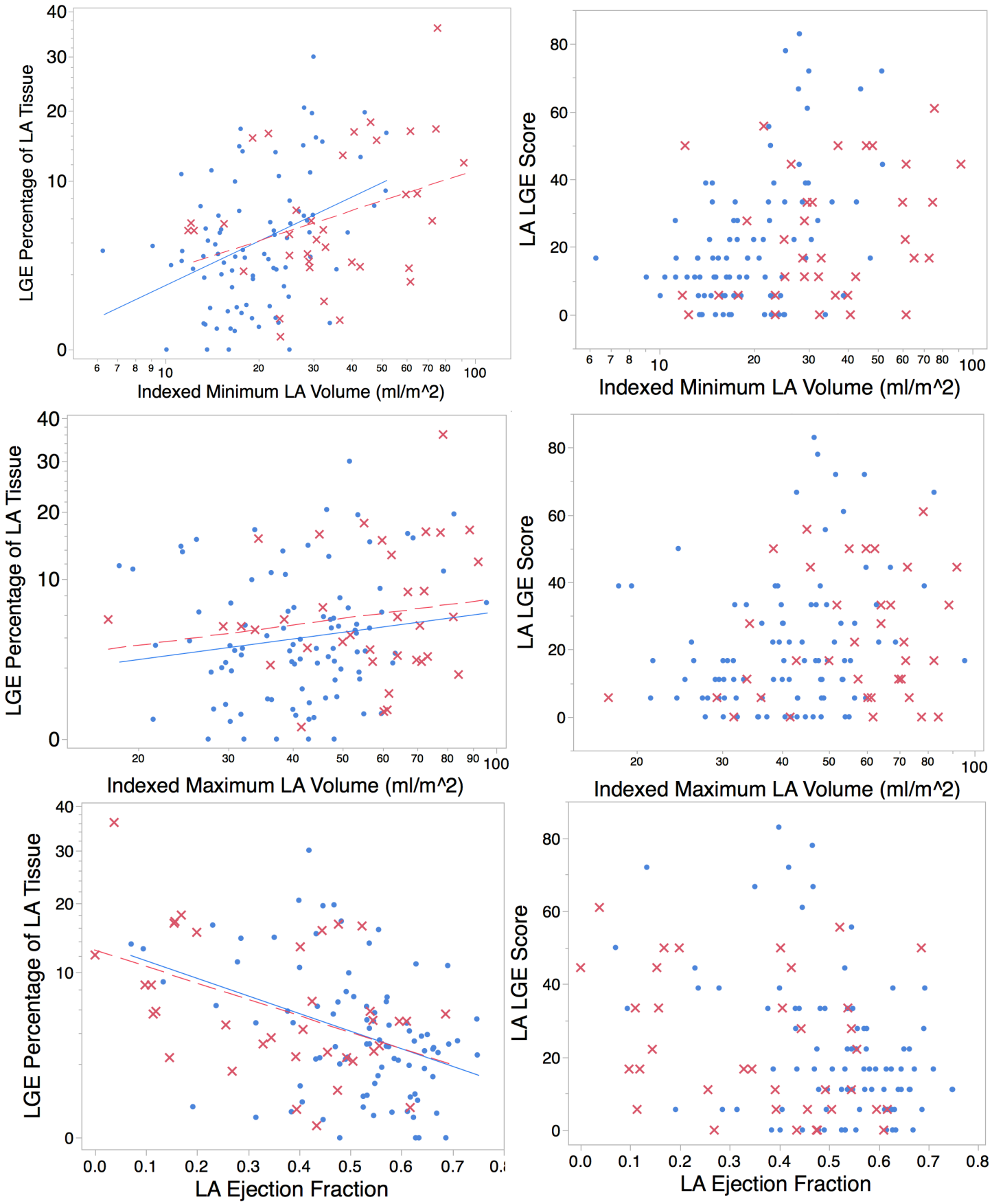

Table 7. Correlation coefficients between LA size and function and measures of LA LGE. Spearman correlations for LGE Score and Pearson correlations for LGE % tissue volume.

	Overall (N=132)				AF (N=36)				Non-AF (N=89)			
	LA LGE Score	p	LA LGE % tissue volume	p	LA LGE Score	p	LA LGE % tissue volume	p	LA LGE Score	p	LA LGE % tissue volume	p
Maximum LA volume	0.240	**0.005**	0.197	**0.022**	0.135	0.433	0.178	0.299	0.235	**0.024**	0.147	0.163
Minimum LA volume	0.346	**<0.001**	0.406	**<0.001**	0.279	0.099	0.349	**0.037**	0.385	**<0.001**	0.401	**<0.001**
LA Ejection Fraction	-0.281	**0.001**	-0.430	**<0.001**	-0.286	0.091	-0.446	**0.007**	-0.271	**0.0104**	-0.375	**<0.001**

Table 8. Correlates of passive LA EF: multivariate analysis with LA LGE and ventricular diastolic filling parameters. (N=42)

	Standardized β	Partial r^2	P
LA LGE Percentage	-0.253	0.137	**0.019**
Ventricular Peak Filling Rate	0.580	0.384	**<0.001**
Time to Peak Filling Rate	-0.199	0.070	0.099
Model r^2		0.610	**<0.001**

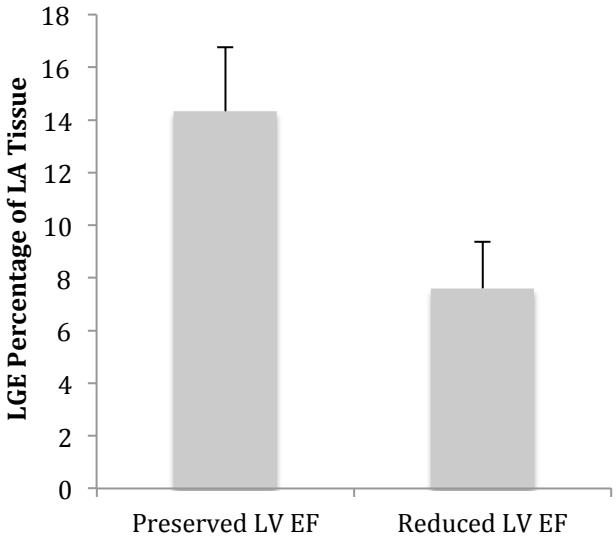

Figure 8. LA LGE in subjects with congestive heart failure. Those with normal or mildly reduced left ventricular EF have greater LA LGE than those with EF < 45% (p=0.032). Data are mean +S.E.

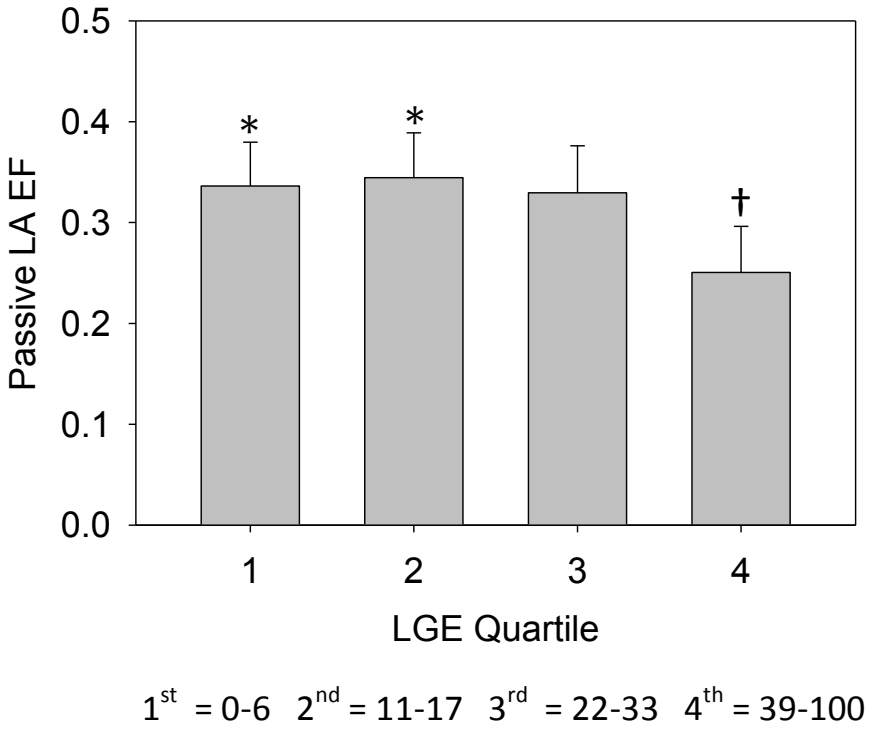

Figure 9. After multivariate adjustment for peak filling rate and time to peak filling rate, those subjects in the quartile with the highest LA LGE score had a significantly lower passive LA ejection fraction than those in the lowest two quartiles (p=0.020).

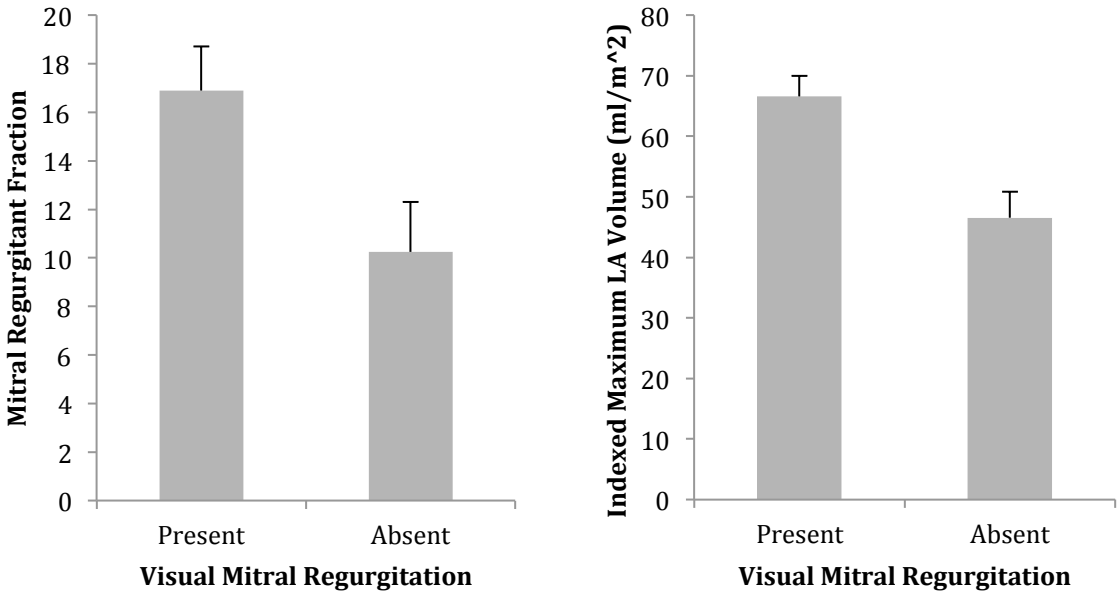

Figure 10. Visualized mitral regurgitation is associated with both a greater measured mitral regurgitant fraction (p=0.022) and indexed maximum left atrial volume (p=0.001).